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Inhibitors to Factor VIII:C in Nonhemophiliacs

To the Editor: The development of inhibitors to factor VIII:C in a nonhemophiliac person is clinically significant due to life-threatening hemorrhagic complications. It occurs predominantly in adults without underlying disease, or it may occur in patients with collagen disease, drug reactions, neoplasms, and other disorders [1]. Measures to control inhibitors consist mainly of treatment of acute bleeding episodes with factor VIII concentrates, corticosteroids, and immunosuppressive drugs as long-term therapy [2–4]. We describe what we believe is the first reported patient with malignant melanoma developing the inhibitor to factor VIII:C.

In a 59-year-old woman who was previously healthy and with uninformative anamnesis, a huge hematoma appeared in the skin of her left wrist, with prolonged bleeding following a tooth extraction in 1988. The patient had been operated on for crural skin melanoma in 1986 and later treated with chemotherapy. She had a normal delivery 30 years earlier. She denied a family history of bleeding. The physical signs of anemia and large arm and thigh hematoma were noted. Clinical findings were otherwise normal. Laboratory data included hemoglobin (Hb) 100 g/L, RBC 3.1×10^{12}/L, WBC 6.7×10^{9}/L, blood urea nitrogen (BUN) 5.2 mmol/L, and alkaline phosphatase 51.5 U/L (normal up to 75 U/L). Bone marrow aspirate and abdominal ultrasound examination were normal. Immunological disorders were excluded. Bone radiography and scintigraphy were normal. Melanin in urine was negative. Hemostatic studies included fibrinogen 3.0 g/L, thrombin time (TT) 16″ (12″), partial thromboplasin time (PTT) 83″ (30″), factor VIII:C 1%, and inhibitor to factor VIII:C 32 Bethesda units/ml. Platelet aggregation with ADP, epinephrine, ristocetin, and collagen was normal. FDP was below 10 γ.

Several times the patient had serious bleeding episodes following venipuncture, sternal puncture, and accidental cut of her hand. The patient was treated with cryoprecipitate, factor VIII concentrate (Hemate-Behring), and activated prothrombin complex within the periods of bleeding. In order to suppress the production of inhibitor, a simultaneous application of factor VIII (1,000 units) and cyclophosphamide (1 g) in five seanses during 1988 and 1989 was also carried out. After initial success, factor VIII decreased again to a value of 1%, with a concomitant increase in an inhibitor titer to 40 Bethesda units. During the period 1988–1989, the patient received six courses of the protocol COP (cyclophosphamide 1 g, vincristine 2 mg, prednisolone 80 mg, 8 days), but without effect. In January 1990, a melanoma reappeared on a distal ulnar epiphysis of 1 × 1-cm diameter. Local irradiative therapy was applied. At that time, factor VIII:C activity was still less than 1% with the inhibitor titer of 45 Bethesda units.

Following completion of radiotherapy, 1,000 units of factor VIII concentrate and 1 g cyclophosphamide was administered each month for an integral period of 14 months. There was a gradual increase in factor VIII:C activity during the period 1990–1991, with a decrease in inhibitor titer. In April 1992, the patient had normal factor VIII:C activity and complete disappearance of the inhibitor. So far there are no signs of melanoma.

Inhibitors may disappear with remission or cure of the underlying disease [1–4]. They may disappear spontaneously even after many years. Green [2] was the first to demonstrate the clinical efficacy of cyclophosphamide and high doses of factor VIII given concomitantly in a patient with the acquired factor VIII inhibitor. In our patient, inhibitor disappeared after 4 years, possibly the result of chemotherapy applied concomitant with factor VIII concentrate.

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Recombinant Interleukin-1 Followed by Immunosuppressive Therapy for Aplastic Anemia

To the Editor: Between October 1991 and February 1993, we treated six patients with severe idiopathic aplastic anemia with recombinant interleukin-1 alpha (rhuIL-1α). Patients ≥10 years of age who had acquired aplastic anemia as defined by the International Aplastic Anemia Study Group were eligible for study [1]. Patients had not received other cytokine therapy for at least 4 weeks prior to study entry. Informed consent was obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Patient characteristics, treatment and response to therapy are summarized in Table I.

The treatment schedule was as follows: rhuIL-1α produced in *Escherichia* coli (Immunex Corp., Seattle, WA) was administered intravenously over 6 hours daily for 5 days. Three patients received daily doses of 0.1 μg/m²/day and 3 patients received 0.3 μg/m²/day. Immunosuppressive therapy was begun a minimum of six days after completing rhuIL-1α (range = 6–17 days). Five patients received horse anti-human thymocyte globulin (ATGAM®, Upjohn Co., Kalamazoo, MI), 15 mg IgG/kg intravenously, and methylprednisolone, 0.5 mg/kg intravenously, daily for 10 days. Two days after completing ATGAM®, oxymetholone (3 mg/kg p.o. daily) was begun and continued for at least 3 months. One patient had oxymetholone discontinued early because of elevated liver function tests. One patient who had a positive skin test to ATGAM® was treated with cyclosporine, 6 mg/kg p.o. BID for 3 months and prednisone, 4 mg/kg p.o. daily for 8 days, followed by a taper over 3 weeks.

Toxicity of rhuIL-1α included fever >38.0°C (n = 4), chills (n = 3), headaches (n = 3), hypertension (transient increase of ≥20 mm Hg) (n = 5), hypotension (systolic pressure <100 mm Hg) (n = 4), myalgias or arthralgias (n = 2), and tachycardia (rate >100/min) (n = 2). All side effects were mild and no patient required attenuation of any rhuIL-1α dose. These side effects are similar to those previously reported [2]. No patient had any change in peripheral counts following completion of rhuIL-1α. Marrow aspirates and biopsies performed one day after completing rhuIL-1α therapy showed no increase in cellularity or change in morphology in five evaluable patients.

Initial response to immunosuppressive therapy was assessed according to previously published criteria [3]. By day 75 two patients had a minimal response and four were nonresponders. All patients except one nonresponder received subsequent therapy (see Table I). No patient has had evidence of evolution to paroxysmal nocturnal hemoglobinuria or a myelodysplastic syndrome. Five patients are surviving 17.1–29.8 months; one died at 22 months from septicemia.